REMARKS

As of the mailing date of the Office Action dated October 18, 2007, claims 37, 40, 41 and 44-46 were pending and under examination. Reconsideration of the instant application in view of the following remarks is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 37 and 41 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Frudakis *et al.* (US Patent 6586570) in view of Weaver *et al.* (2002/0165180). Specifically, the Action asserts that Frudakis *et al.* teach a first oligonucleotide and a second oligonucleotide wherein the first oligonucleotide and the second oligonucleotide hybridize to a first and second polynucleotide, wherein the first and second polynucleotide comprise a sequence of SEQ ID NO:7. The Action admits that Frudakis *et al.* do not teach oligonucleotides or oligonucleotide pairs that hybridize to SEQ ID NO:75 but asserts that this deficiency is remedied by Weaver *et al.* Weaver *et al.* allegedly teaches genes that are up-regulated in cancer cells and that the gene pattern resulting from these genes is indicative of a cancerous state. The Action therefore concludes that one of ordinary skill at the time of the claimed invention would have been motivated to provide a composition comprising oligonucleotides which hybridize to a sequence comprising SEQ ID NOs:7 and 75 for the benefit of providing gene patterns indicative of a cancerous state and for developing potential antitumor agents as suggested by Weaver *et al.*

Applicants respectfully traverse the ground for rejection and submit that the presently claimed methods are not obvious in view of the cited art. In particular, Applicants submit that the cited references taken for what they teach as a whole do not teach or suggest the presently claimed compositions for detecting breast cancer. In particular, Applicants submit that, contrary to the Action's assertions, Frudakis *et al.* do not teach a first oligonucleotide and a second oligonucleotide wherein the first oligonucleotide and the second oligonucleotide hybridize to a first and second polynucleotide. This reference only teaches oligonucleotides that hybridize to a single polynucleotide. The sections of Frudakis *et al.* cited in the Action (col. 9, lines 26-29 and col 14) refer only to generic primer language and refer only to single oligonucleotides that hybridize/detect a single sequence at a time, not multiple oligonucleotide

sequences used to detect multiple, complementary breast cancer marker sequences simultaneously. Further, column 21, lines 27-50 referred to in the Action actually describes an experiment where different splice forms of the same gene are detected and the experiment, in fact, shows that all the splice forms have the same expression pattern:

> In further studies, several different splice forms of the antigen B11Ag1 (also referred to as B305D) were isolated, with each of the various splice forms containing slightly different versions of the B11Ag1 coding frame. Splice junction sequences define individual exons which, in various patterns and arrangements, make up the various splice forms. Primers were designed to examine the expression pattern of each of the exons using RT-PCR as described below. Each exon was found to show the same expression pattern as the original B11Ag1 clone…(column 21, lines 27-35; emphasis added).

Thus, the different splice forms of the gene described are not complementary one to the other with regard to detection of breast cancer. Accordingly, using multiple oligonucleotides to detect the multiple splice forms would detect no more cases of cancer than using a single oligonucleotide directed to one of the splice forms, thus teaching away from the present invention.

Further, as admitted by the Action, Frudakis *et al.* do not teach or even suggest the polynucleotide of SEQ ID NO:75 let alone that compositions comprising oligonucleotides to detect this sequence in combination with the polynucleotide of SEQ ID NO:7, or any other marker, to better detect cancer. The Action relies on Weaver *et al.* to remedy this deficiency. However, Weaver *et al.* do not teach or suggest the polynucleotide of SEQ ID NO:7, its breast cancer expression pattern, nor that compositions comprising oligonucleotides to detect this sequence in combination with the polynucleotide of SEQ ID NO:75, or any other marker, can be used to better detect breast cancer.

The present invention centers on the discovery that when these two (or more) markers are used together, they provide expanded detection of breast cancer (see, *e.g.*, the specification as filed, Table 3, Table 6, Example 7). There is no indication in Frudakis *et al.* or in Weaver *et al.* that these cancer-associated markers complement one another and provide

expanded cancer detection when used together. Thus, Applicants submit that the skilled artisan, at the time of filing of the present invention, would not have had the requisite reasonable expectation that the combination of the individual breast cancer markers disclosed by Frudakis *et al.* and Weaver *et al.* would have provided any benefit whatsoever over any of the markers used individually.

Moreover, the United States Supreme Court recently noted that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.*, 550 U.S. __, 383 U.S. 39, 53-54 (April 30, 2007, No. 04-1350). Applied to the instant application, Applicants submit that even assuming *arguendo* that there was motivation to combine the independent elements of the cited Frudakis *et al.* and Weaver *et al.* references, such a combination unquestionably falls short of rendering obvious the presently claimed compositions for detecting the presence of breast cancer cells by detecting multiple cancer-associated markers. Nothing in the prior art would have permitted the person having ordinary skill to reasonably predict that the combination of the individual recited cancer-associated markers would provide the advantages of the presently claimed method.

Additionally, "[t]he Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a *predictable* result." *KSR*, citing *U.S. v. Adams*, 383 U.S. 39, 50-51 (1966) (emphasis added). It is respectfully submitted that the subject matter of the instant claims simply could not have been predicted by the prior art, where neither Frudakis *et al.* or Weaver *et al.* each alone or in combination with any other knowledge in the prior art, provide the requisite reasonable expectation of success to the person of ordinary skill. On this point, prior to the instant application, it could not be predicted, *e.g.*, whether the detection of the recited cancer-associated markers combined would provide additional benefit over detection of each individually. As articulated by the Supreme Court, the presently recited combination thus does "more than yield a predictable result," and is therefore nonobvious.

There is simply no indication in the prior art that the recited markers complement one another in their ability to detect breast cancer in a biological sample. The skilled artisan

would have had no way of knowing that combining the recited markers would provide any advantage whatsoever. Contrary to the Action's assertion, without the teachings of the present application, choosing and combining individual cancer-associated markers as taught in the cited art could have resulted in no added advantage in detection of breast cancer and could, in fact, have resulted in an increase in expense and time. Without the teachings of the present application, the skilled artisan would have had no way to reasonably predict whether the combination of these cancer-associated markers would be advantageous.

Claims 44 and 46 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Frudakis *et al.* (US Patent 6586570) in view of Weaver *et al.* (2002/0165180), in view of Shimkets *et al.* (WO 01/47944) and further in view of Buck *et al.* (Biotechniques, Vol 57, pages 528-536; September 1999). Specifically, while the Action admits that Frudakis *et al.* and Weaver *et al.* do not teach the specific primers of SEQ ID NOs:53-57, the Action relies on Shimkets *et al.* and Buck *et al.* to remedy this deficiency. In particular, the Action asserts that Shimkets *et al.* teach a primer sequence of SEQ ID NO:51 that is 80% identical and differs from the recited SEQ ID NO:53 by the addition of a few bases at the 5' and/or 3' end. (Applicants note that the sequence shown at page 5 of the Action corresponds to SEQ ID NO:630 of Shimkets *et al.* not SEQ ID NO:51). Similarly, claim 45 is rejected over Stemmer *et al.* (US Patent 6489146) further in view of Buck *et al.* The Action asserts that Stemmer *et al.* teach a composition comprising a sequence comprising 12 consecutive nucleotides that are identical to the sequence of SEQ ID NO:57 and that the primer taught by Stemmer *et al.* (SEQ ID NO: 36) only differs by the addition of a few bases at the 5' and/or 3' end. The Action asserts that the skilled artisan would have had a reasonable expectation of success in using an equivalent primer to those taught by Shimkets *et al.* and Stemmer *et al.* given the teachings of Buck *et al.*

Applicants respectfully traverse this ground for rejection. Frudakis *et al.* and Weaver *et al.* are discussed above. As admitted by the Action, Applicants submit that Shimkets *et al.* and Stemmer *et al.* do not teach even the recited oligonucleotides of SEQ ID NOs:53 and 57. The primers taught by these references not only differ by numerous residues on either end of the oligonucleotide but the added residues on either end are not complementary to the target

sequences of SEQ ID NOs:7 and 75. The Action asserts that the skilled artisan would have a reasonable expectation of success in using an equivalent primer based on the teachings of Buck *et al.* Applicants respectfully disagree and submit that Buck *et al.* describe the design and use of sequencing primers. The oligonucleotides recited in SEQ ID NOs:53 and 57 as presently claimed, are PCR primers that were designed and optimized to specifically and exclusively detect by amplification cDNA of SEQ ID NOs:7 or 75 and to exclude corresponding genomic DNA from amplification (see *e.g.*, Example 11 and Table 7 of the specification as filed). Thus, that all of the primers tested by Buck *et al.* worked in the setting of DNA sequencing simply has no relevance whatsoever to the specific detection by amplification of SEQ ID NOs:7 and 75.

Moreover, contrary to the assertions of the Action, the skilled artisan would not be motivated to combine the teachings of Buck *et al.,* which, as noted above, relate solely to sequencing primers, to modify the oligonucleotides taught in either Shimkets *et al.* or Stemmer *et al.* to arrive at Applicants' invention, nor would the skilled artisan have any reasonable expectation of success of arriving at Applicants' invention by doing so. In particular, as would be readily recognized by the skilled artisan, the additional nucleotides present in the oligonucleotides taught by Shimkets *et al.* and Stemmer *et al.* are at the key 3' end necessary for specific amplification and also are not complementary to the recited polynucleotides of SEQ ID NOs:7 or 75. As would be understood by the skilled artisan, the addition of noncomplementary nucleotides to the 3' end of either of the presently recited primers would abrogate specific amplification of the genes of interest and further would not function to specifically exclude genomic DNA. Thus, the skilled artisan would have had absolutely no reason or motivation to use the primers taught by Shimkets *et al.* and Stemmer *et al.,* with or without the teachings of Buck *et al.,* for the amplification of the presently recited SEQ ID NOs:7 and 75 and, more importantly, based on basic principles of DNA amplification known in the art, would have had no success, let alone a reasonable expectation of success, in amplifying cDNA of SEQ ID NOs:7 and 75 using such primers. Therefore, Applicants submit that, contrary to the assertions of the Action, the equivalency of the primers taught by Shimkets *et al.* and Stemmer *et al.* and those of the present invention is not at all established in the prior art. Furthermore, the skilled artisan

would readily appreciate that the components at issue are, in fact, NOT functional or mechanical equivalents.

Accordingly and in view of the foregoing, Applicants submit that the instant claims satisfy the requirements of 35 U.S.C. § 103. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above remarks, the claims are now believed to be in condition for allowance. However, should any further issue require attention prior to allowance, the Examiner is requested to contact the undersigned at 206-622-4900 to resolve same.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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